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(54) Title: AMINOALKYL-BENZOFURAN-5-OL COMPOUNDS FOR THE TREATMENT OF GLAUCOMA

(57) Abstract: The present invention provides novel compounds, compositions containing the compounds of the invention in a pharmaceutically acceptable excipient and methods for using the compositions for lowering intraocular pressure.

AMINOALKYL-BENZOFURAN-5-OL COMPOUNDS FOR THE TREATMENT OF GLAUCOMA

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to treatment for lowering intraocular pressure and to compounds for use in such treatments. More particularly, the present invention relates to the use of compounds with serotonergic 5-HT5-HT_2 agonist activity to lower intraocular pressure (IOP), treat glaucoma, and to provide neuroprotection.

2. Description of the Related Art

Serotonin (5-hydroxy tryptamine; 5-HT5-HT) is an endogenous biogenic amine with a well defined neurotransmitter function in many tissues of the body including the eye [Zifa and Fillion 1992; Hoyer *et al.* 1994; Tobin *et al.* 1988].

5-HT is known to interact with at least seven major 5-HT receptors (5-HT_1 - 5-HT_7) and additional subtypes within these families to initiate intracellular biochemical events such as stimulation of second messengers (e.g. cAMP, inositol trisphosphate) eventually leading to the final biological response, for example, tissue contraction or hormone release, etc. [Hoyer *et al.* 1994; Martin *et al.* 1998]. Receptor subtypes within the 5-HT_1 family are negatively coupled to adenylyl cyclase (AC) and cause inhibition of cAMP production, while 5-HT_4, 5-HT_6, and 5-HT_7 receptors are positively coupled to AC and thus stimulate cAMP production when activated by 5-HT [Martin *et al.* 1998]. The receptors in the 5-HT_2 family are positively coupled to phospholipase C (PLC) and thus

generate inositol phosphates and mobilize intracellular calcium when activated to mediate the effects of 5-HT. The 5-HT_3 receptor is unique in that it couples to an ion channel which gates sodium, potassium, and calcium [Hoyer *et al.* 1994].

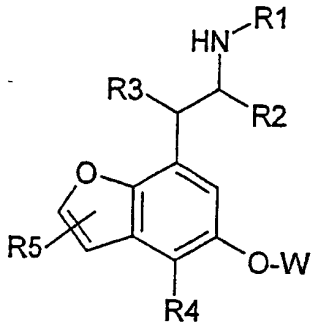
The human and animal 5-HT_7 receptor has only recently been cloned, expressed, and shown to be present in various brain areas and peripheral tissues [Eglen *et al.* 1997]. Recent studies have shown there to be four splice variants of the 5-HT_7 receptor [Heidmann *et al.* 1997]. It has been proposed that the 5-HT_7 receptor may be involved in the pathophysiology of sleep disorders, depression, and other psychiatric disorders [Eglen *et al.* 1997]. In the periphery, stimulation of 5-HT_7 receptors results in relaxation of blood vessels and hence vasodilation [Eglen *et al.* 1997].

Known compounds exhibiting 5-HT_2 agonist activity have typically been designed to treat numerous central nervous system (CNS)-related conditions, particularly the treatment of obesity and depression, by activation of 5-HT_{2C} receptors. Thus, one desired property of known 5-HT_2 agonist compounds is that they easily penetrate the blood brain barrier. Compounds possessing the property of penetration into the CNS generally do not contain polar groups.

To treat ocular diseases, it is desirable to administer compositions orally or topically that will remain in the ocular tissues and not cross the blood brain barrier to enter the CNS. What are needed are 5-HT_2 agonist compounds that are useful in the treatment of ocular diseases characterized by an elevated intraocular pressure, the treatment of glaucoma and neuroprotection. Such compounds would not have a propensity to cross the blood brain barrier.

SUMMARY OF THE INVENTION

The present invention overcomes these and other drawbacks of the prior art by providing compounds having 5-HT_2 agonist activity that do not cross the blood brain barrier. More specifically, the present invention provides compounds having the following general formula:



wherein R^1 is hydrogen or C_{1-4}alkyl; R^2 is hydrogen, C_{1-4}alkyl, or R^1 and R^2 can together be $(CH_2)_{2-4}$ to complete a heterocyclic ring; R^3 is hydrogen, hydroxyl, C_{1-4}alkoxy, or fluorine; R^4 is selected from C_{1-4}alkyl, halogen, nitrile, C_{1-6}alkylthiol, trifluoromethyl, C_{1-4}alkyl substituted by HO or C_{1-3}alkoxy, R^5 is hydrogen, halogen, C_{1-4}alkoxy, nitrile, W is hydrogen or $C(=O)C_{1-8}$alkyl. In preferred embodiments, R^1, R^3 and R^5 are hydrogen, R^2 is methyl, R^4 is halogen, methyl or trifluoromethyl, and W is hydrogen. Most preferably, the compounds of the invention have an R-configuration at the carbon atom bearing the primary amine.

In another aspect, the present invention provides compositions containing the compounds described above in a pharmaceutically acceptable excipient. The compositions are most preferably in the form of topical ophthalmic formulations for delivery to the eye. The compounds of the invention may be combined with ophthalmologically acceptable

preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution to form the compositions of the invention.

The compositions of the invention are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The compounds of the invention as

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